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Edwards Angell Palmer & Dodge LLP
111 HUNTINGTON AVENUE
BOSTON, MA 02199

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,357	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49,50,52,53 and 56-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49,50,52,53 and 56-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/26/08 has been entered.

Claim Rejections - 35 USC § 112

2. Claims 49, 50, 52, 53, 56, 57, 58, 59 and 60-77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention

The invention of claim 49 is expressly drawn to a method detecting rheumatoid arthritis in a human test subject. The claims all include a step of quantifying a level or RNA encoded by a cell division cycle associated 1 (CDCA1) gene in a blood sample obtained from said human and comparing the level with a quantified level of RNA encoded by said gene in blood samples of control subjects which are classified as healthy control subjects, also comparing the test level with a quantified level of control RNA encoded by said gene in blood samples of control subjects which are classified as having rheumatoid arthritis and wherein said comparison of a statistically significant determination resulting from steps the comparisons that expression of said gene in

said sample of said test subject is different relative to said samples of said control subjects classified as healthy control subjects, and is similar relative to said samples of said control subjects classified as having rheumatoid arthritis is indicative of rheumatoid arthritis in said human test subject.

Claim 58 is drawn to a method for detecting expression of a gene encoding a cell division cycle associated 1 (CDCA1) in a human "test subject." Claims which depend from claim 58 set forth that the detected expression is quantified and compared to quantified level of control RNA encoded by said gene in blood samples of control subjects. Listed control subjects include healthy subjects. Further dependent claims set forth steps of classifying or identifying the test subject as being a candidate for having rheumatoid arthritis depending on the outcome of the comparing steps. Thus, it is clear that the intended use of claim 58 and those that depend from claim 58 is for classifying or identifying the test subject as being a candidate for having rheumatoid arthritis.

Claim 66 is drawn to a method of screening a human test subject "for being a candidate for having rheumatoid arthritis" and includes similar steps of detection of the CDCA1 gene in a blood sample, quantifying the expression and comparing the level to a quantified level of control RNA encoded by said gene in blood samples of control subjects classified as healthy subjects, where said test subject is a candidate for RA if said level of RNA encoded by said gene in said blood of said human is significantly different relative to that of said control subjects classified as healthy subjects with a p value of less than 0.05.

In claim 70, the invention is drawn to a method a method for classifying CDCA1 gene expression in a human, and sets forth steps of quantifying a level of RNA encoded by a CDCA1

gene in a test subject, comparing that level to a level of RNA found in blood samples from control subjects having rheumatoid arthritis and also comparing it to control subjects who are healthy. The independent claim states that based on particular determinations, the classification of CDCA1 gene expression results either with that of said subjects having rheumatoid arthritis or with that of subjects who are healthy.

The nature of the invention requires the knowledge of a reliable relationship between CDCA1 expression in blood and the presence of or indication of rheumatoid arthritis. Further, the practice of the invention requires an understanding of how the presence of rheumatoid arthritis effects the level of CDCA1 expression in human blood. The practice of the invention requires an understanding of how the presence of rheumatoid arthritis effects the level of CDCA1 expression in human blood in patients having rheumatoid arthritis versus patients that do not have rheumatoid arthritis but may have some other disorders. The nature of the invention requires the knowledge of a reliable association between CDCA1 expression and the ability to classify a particular individual's expression with the expression of subjects having rheumatoid arthritis or not having rheumatoid arthritis, and further, the use of this method requires that there is an underlying assumption that this classification is meaningful. Reading the claims in light of the specification it is clear that applicant intends to use such a classification method in order to provide a tool that is used as part of a diagnostic process, and such a use requires the knowledge of a reliable association underlying the classification.

Many of the claims additionally require a step of comparing the level of RNA detected in a test subject to "a quantified level of control RNA encoded by said gene in blood samples of

control subjects." To practice these claims, it is essential to know the quantified level of control RNA encoded by said gene in blood samples of control subjects.

Scope of the claims

Many aspects of the claims remain quite broad.

The claims are very broad in scope because they encompass that ANY level and direction of difference in gene expression between the healthy controls or the controls not having rheumatoid arthritis is indicative of said rheumatoid arthritis, if that difference is "statistically significant." That is, the claims do not set forth that one level should be higher or lower than the other, and further do not set forth how much of a "difference" between two individuals would be necessary to draw the conclusions set forth in the claims.

Teachings in the Specification/Examples

Regarding rheumatoid arthritis, the specification provides example 20 wherein gene expression profiles of blood samples from individuals having rheumatoid arthritis were compared with normal individuals, that is healthy patients. The specification teaches that 2,068 genes were identified as being differentially expressed, and regarding the instant claims, table 3M provides a list of these genes (Example 20). CDCA1 is among the genes.

The table lists genes that were differentially expressed, but does not provide any further information. For example, the tables do not teach if the expression was higher or lower in rheumatoid arthritis patients versus controls.

The specification does not provide any guidance as to the level of "difference" that is sufficient (1 fold, 2 fold, etc) to result in a conclusion that rheumatoid arthritis is detected, nor

does the specification provide any guidance as to the direction of the difference (higher or lower expression) that is expected to be observed for any single pairing of samples.

The specification fails to provide information about an essential aspect of the invention, namely, the nature of the difference in expression that was observed between rheumatoid arthritis patients and healthy patients. Furthermore, though the specification teaches that this gene is differentially expressed in rheumatoid arthritis patients versus healthy patients, the specification teaches this is true for thousands of genes. There is no guidance or analysis of data in the specification to suggest that this gene in particular, and considered in isolation, is sufficient to conclude that rheumatoid arthritis is present in a sample, as is instantly claimed. This information is essential to understanding and practicing the claimed invention because it is critical to knowing how to interpret a particular comparison result.

State of the Prior Art and Level of Unpredictability

The expression of genes the example was tested by hybridization of samples to a microarray that contains genetic information for tens of thousands of genes. This technology area is highly unpredictable, and as a result significant guidance is required to practice inventions using this type of data. Lee (Clinical Chemistry, 47:8, 1350-1352 (2001)) teaches that despite the technical accuracy of individual observations on an array, these data "are much more prone to numerous false-positive findings fundamentally because of (a) an extremely large number of observations and (b) a very wide dynamic range of gene expression values obtained from gene chip experiments." In view of these unpredictable aspects of applying such data, Lee teaches that replication is necessary to begin to screen out false positive results. There is no replication in the instant specification.

Observing differences in expression between two populations is a highly unpredictable endeavor. For example, while the specification demonstrates that this gene was differentially expressed in the samples collected, the specification does not undertake analysis to see if this gene is differentially expressed in the blood of patients having other autoimmune diseases. Thus, if one were to detect expression of CDCA1 in blood that is different from healthy patients, it would be highly unpredictable if this difference is due to the presence of rheumatoid arthritis in particular or some other disease or condition. It is highly unpredictable how would one begin to know if that level of expression indicated rheumatoid arthritis, SLE, both, one but not the other, something in between or even some other condition or disorder for which the expression profile has not yet been determined.

Furthermore, although CDCA1 was not observed to be differentially expressed in any of the other examples in this specification, it is unknown and unpredictable whether it would be expressed in the blood of patients having other autoimmune diseases or any other diseases which were not tested in the instant specification or diseases which were tested in the instant specification but in a different population of test subjects, and whether this expression would be different from levels of expression in healthy controls. A method for detection which relies on a comparison between expression in the blood of a test subject and control subjects requires the knowledge of this information in order to reliably "detect" rheumatoid arthritis, as set forth in the claims. The instant specification has not established that all difference, no matter the magnitude nor the direction, relative to any control subjects or even relative to a healthy control subject is indicative of rheumatoid arthritis. It is not known under what circumstances the result observed in the instantly examined control and test populations would be repeatable, as the results have

not been validated. But even if one were to obtain the same result, it would be unknown because applicant did not disclose the magnitude of difference in expression between rheumatoid arthritis patients or controls, nor did applicant disclose the direction of variation. All of these inquiries are particularly important in this case since the specification is silent as to which differential expression observations would be sufficient to detect the presence of rheumatoid arthritis.

In the post-filing art, Osman et al. provide an analysis which includes microarray hybridization of test and control isolated from total cellular RNA where the test is patients with bladder cancer and the control is healthy individuals (Osman et al. Clinical Cancer Research 2006; 12(11) 3371-3380). Although Osman et al. are analyzing bladder cancer and not rheumatoid arthritis, they provide some cautionary guidance regarding their study which could equally and fairly be applied to the study provided to support the instantly claimed invention. Osman et al. teach that their study has several limitations including that "the expression profiles may represent the activation of specific immunologic response to the presence of bladder tumors, and that the profiles identified in this study may be intrinsic to the cohort of patients evaluated in this study (p. 3379)." The field remains highly unpredictable years after the filing of the instant application, even with the significantly more guidance given in this post-filing date reference.

Further, the claims of the instant application set forth the comparison of the gene expression in a single individual versus as few as two other individuals, and they set forth that a comparing gene expression between the two is "indicative of" rheumatoid arthritis. Neither the specification nor the claims set forth a threshold of difference between an individual's expression and the control expression of CDCA1 in the blood that would be sufficient to conclude that the difference in gene expression between a test individual and any type control group is "indicative

of" any of the recited rheumatoid arthritis. Because the claims encompass any level of altered gene expression, it is relevant to point out that the art of Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a rheumatoid arthritis or the absence of rheumatoid arthritis.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression

is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). There is no replication of data in the instant specification.

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention. In particular, the specification does not provide adequate guidance to appraise one of ordinary skill in the art as to what levels of CDCA1 gene expression must be observed to successfully conclude that rheumatoid arthritis is present. Further, although the specification teaches there are differences in CDCA1 levels in a rheumatoid arthritis population versus a control patient population, the specification is silent as to the nature of the "difference" in magnitude or direction. Thus, given the lack of teaching in the specification and the highly unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

In order to practice the claimed invention, one would have to undertake an extensive amount of experimentation in a highly unpredictable technology area. One would begin by trying to reproduce the results observed in the instant specification to determine if there is a relative upregulation or downregulation of CDCA1 in rheumatoid arthritis patients versus healthy control patients, as the specification does not even provide this minimal guidance. Without this knowledge one would not even begin to know how to interpret any results obtained in practicing the claimed methods. For example, consider the comparison of a test result and a control population of healthy individuals. How different from the average level of expression of healthy individuals would the test result have to be to indicate rheumatoid arthritis? Would any difference, up or down regulation be indicative of rheumatoid arthritis? Or could one indicate

rheumatoid arthritis and one a different disease or condition, such as lupus? Is CDCA1 expressed differently in the blood of individuals with a disease other than lupus and rheumatoid arthritis relative to control populations? Is this expression also diagnostic of other autoimmune diseases or other or other disorders entirely unrelated to rheumatoid arthritis? In order to reliably use a method for detecting rheumatoid arthritis, one would first have to answer at least these questions. One would also, however, have to carry out this testing for validation, for it is possible that the result observed in the instant specification is intrinsic to the cohort of patients evaluated in applicant's study. Further, one would have to undertake experimentation to determine difference thresholds required to determine that a patient has or does not have a disease.

As discussed, this art area is highly unpredictable.

Conclusion

The claims include methods which encompass the detection in blood of the expression of CDCA1 in a test subject and comparing this expression to control subjects, wherein the comparison itself "is indicative of rheumatoid arthritis." The identification of gene differential expression/disease indication relationships is a highly unpredictable endeavor, requiring extensive experimentation. The specification provides minimal guidance. In light of the factors discussed, therefore, it is concluded that it would require undue experimentation to practice the claimed invention.

Although some of claims are drawn to a method of "detecting expression" or "classifying expression," and not to diagnosis or identifying increased likelihood of disease or the like, it is critical to understand how the classification can be used in order use the claimed invention. In

this case, the specification does not provide sufficient guidance as to how to use the detecting or classification methods other than in methods that are directed towards diagnostic purposes. What is the meaning of classifying expression "with that of subjects having" rheumatoid arthritis or with subjects who are healthy? While one could do the method steps as written, thus satisfying the "how to make" aspect of 112 1st paragraph, the specification does not provide sufficient disclosure to satisfy the how to use aspect of the requirement.

The data in the specification is not replicated. As discussed in the rejection, it is established that the technology on which the instant claims is based is a highly unpredictable technology, and in the face of such a high level of unpredictability, replication is necessary before results can be considered sufficient to support claims directed at classifying the gene expression of an individual test subject. Therefore, even this claim, after having considered all of the factors set forth in this rejection, lacks proper enablement.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 58, 60, 61, 62, 63, 67, 68, 69, 71, 72, 73, and 75, are rejected under 35 U.S.C. 102(a) and 102(b)as being anticipated by William Chittenden, dissertation submitted to the faculty of Virginia Polytechnic Institute and State University, August 2002.

5. These claims are not fully supported under 112 1st paragraph in the instant application nor any of the previously filed applications for at least the reasons discussed in this office action. This reference is applied under 102(a) and 102(b). If applicant establishes support for the claimed invention to a prior application such that the 102(a) and/or 102(b) does not apply the rejection will be withdrawn.

Chittenden teaches quantification and analysis of gene expression in mRNA isolated from whole blood, by isolating cells, precipitating RNA, producing cRNA and hybridization with the probe array HG-U133A, quantification of hybridization and calculation of differential expression. It is an inherent property of this array that it contains probes to CRSP6, and thus, the method taught by Chittenden is a method which uses an oligonucleotides of predetermined sequence which are specific for CRSP6. This chip also inherently has thereupon housekeeping genes that are used for quantifying expression. Further Chittenden tests individuals with disease and healthy controls (p. 58-59, 62-66). Chittenden does not specifically discuss CDCA1 expression, but it would have inherently been detected in the blood of healthy controls by the hybridization and array reading methods.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 58, 60, 61, 62, 63, 65, 67, 68, 69, 70, 71, 72, 73, 75, and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maas et al. (The Journal of Immunology, July 1, 2002,

Vol. 169, pages 5-9) in view of Affymetrix GeneChip Human Genome U133 Set datasheet, 2001.

Maas et al. teach a method for detecting the expression of genes in blood from individuals having rheumatoid arthritis and patients not having rheumatoid arthritis (healthy controls) which includes isolating total RNA from a whole blood sample, processing it, hybridizing it to a microarray, quantifying the expression and identifying differentially expressed genes. Maas et al. detected genes which were differentially expressed between patients having RA and healthy control patients, and classify gene expression as being with the patients who have rheumatoid arthritis or healthy controls based on the level of difference of expression observed between the two types of samples.

The content of the array (Research Genetic GF-211 membranes) used by Maas et al. was not available to the examiner at the time of writing this office action, but this array included probes to a number of different coding genes. This chip also inherently has thereupon housekeeping genes that are used for quantifying expression, and at the time the invention was made it was routine to detect gene expression relative to a housekeeping gene. It is unknown if CDCA1 was among those genes.

However, at the time the invention was made, Affymetrix had provided the GeneChip Human Genome U133 Set which included CDCA1 among the genes which are detected by the array. It would have been prima facie obvious to one of ordinary skill in the art to have substituted the Affymetrix gene chip for the one used by Maas et al. Because both references teach arrays that are useful for detecting gene expression in a wide variety of genes, with the Affymetrix array providing means to detect over 38,000 transcripts, it would have been obvious

to one of ordinary skill in the art to have substituted one array for another to achieve the predictable result of detecting the expression of many different genes in the blood of individuals having RA versus controls. Such a substitution would have inherently and necessarily resulted in the detection and quantification of CDCA1 in the blood samples of the patients having RA and the healthy control patients.

8. Claims 58, 60, 61, 62, 63, 65, 67, 68, 69, 70, 71, 72, 73, 75, and 77, are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al. (PNAS USA Vol. 94, p. 2150, March 1997) in view of both Affymetrix GeneChip Human Genome U133 Set datasheet, 2001 and Sharma et al. (WO 98/49342; cited in IDS).

Heller et al. teach a method for detecting the expression of genes in a sample from individuals having rheumatoid arthritis and patients not having rheumatoid arthritis (healthy controls) which includes isolating total RNA from a the sample, processing it, hybridizing it to a microarray, quantifying the expression and identifying differentially expressed genes. Heller et al. detected genes which were differentially expressed between patients having RA and healthy control patients, and classify gene expression as being with the patients who have rheumatoid arthritis or healthy controls based on the level of difference of expression observed between the two types of samples.

Heller et al. do not teach the use of an array which includes probes for CRSP6.

However, at the time the invention was made, Affymetrix had provided the GeneChip Human Genome U133 Set which included CDCA1 among the genes which are detected by the array. This chip also inherently has thereupon housekeeping genes that are used for quantifying expression, and at the time the invention was made it was routine to detect gene expression

relative to a housekeeping gene. It would have been prima facie obvious to one of ordinary skill in the art to have substituted the Affymetrix gene chip for the one used by Maas et al. Because both references teach arrays that are useful for detecting gene expression in a wide variety of genes, with the Affymetrix array providing means to detect over 38,000 transcripts, it would have been obvious to one of ordinary skill in the art to have substituted one array for another to achieve the predictable result of detecting the expression of many different genes in the blood of individuals having RA versus controls. Such a substitution would have inherently and necessarily resulted in the detection and quantification of CDCA1 in the blood samples of the patients having RA and the healthy control patients.

Heller et al. in view of the Affymetrix product sheet do not teach detecting applying their analysis to the gene expression in a blood sample, and in particular detecting CDCA1 in a blood sample.

Sharma et al. teach that from the very early stages of diseases the whole organism response to the changed condition (p. 10, 4th full ¶). In light of this, Sharma et al. teach a method for identifying a marker useful for diagnosing a disease comprising the steps of detecting the presence of RNA in an unfractionated sample of whole blood from each of one or more subjects having said disease and quantifying a level of said RNA in said sample. Namely, Sharma et al. teach the preparation of gene transcript patterns beginning with extraction of mRNA from tissues, cells or body parts of an individual or organism which has a disease or condition (p. 7, final ¶, p. 12, 1st ¶), and particularly teach the isolation of mRNA from unfractionated whole blood samples, where unfractionated is interpreted as meaning that the cell types within blood were not separated from one another (p. 35, section 5.1.1). Sharma et al.

teach quantifying the level of expression and determining a difference between the quantified level in the sample from the diseased subject and a similarly quantified level of genes of control RNA from an unfractionated sample of whole blood from each of one or more first control subjects (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Sharma et al. teach that these methods are carried out by producing amplification products from RNA extracted from an unfractionated sample of whole blood (p. 18 and p. 35, Example 5). Sharma et al. specifically suggest that this method can be applied to the study of schizophrenia (p 6, 3rd ¶).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Heller et al. in view of the Affymetrix product sheet so as to have additionally tested the blood of the patients having RA and the healthy control samples. One would have been so motivated by the express teachings of Sharma et al. that disease exerts a global effect on individuals and that this effect can be measured by gene expression in the blood. The identification of markers for disease in the blood suggests a potential minimally invasive method to detect this disorder. One would have been motivated to continue to use the microarray analysis taught by Heller et al. in view of the Affymetrix product sheet since the use of the microarray enables large scale screening of many different human genes, and Sharma et al. expressly teach that marker genes may be identified by differential hybridization methods, which Heller et al. in view of the Affymetrix product sheet use (see Sharma, paragraph bridging pages 4-5).

Response to Remarks

Applicant traverses the rejection for lack of enablement.

Applicant summarizes the claims on pages 9-10.

Applicant states that neither the magnitude nor direction of the expression of the CDCA1 are required to enable one of ordinary skill in the art how to make and/or use the claimed invention. instead what is required is at least one method for enabling the invention, which is provided in the way of identifying statistically significant differently expressed genes at a threshold of $p<0.05$. Applicant reiterates that the specification has discovered an association between CDCA1 expression and rheumatoid arthritis (RA), and that the disclosure supports the instantly claimed methods. The reasons that the examiner disagrees with this assertion are set forth in the rejection. Applicant disclosed that a difference in expression was identified but failed to disclose the nature of the difference. All of the claims require comparing the level of expression with quantified levels from control subjects, but the specification provides no guidance at all as to what these levels are. Based on the teachings of the specification, one would have to begin again applicant's experimentation. Since the nature of the control values are entirely unpredictable based on applicant's disclosure, one would have to determine these values, then validate them. This is not simply routine experimentation since the technology of establishing a relationship between gene expression and a phenotype is an empirical and unpredictable technology. This is a critical feature of the claimed invention, and a significant lack of disclosure. Complete reasoning for maintaining the rejection is given in the rejection.

On page 11 applicant states that methods and protocols for applying differentially expressed genes to indicate the presence of a disease or condition regardless of direction of change of expression are well established. Applicant cites Slonim who states that the most basic question one can ask is which genes expression levels change significantly. It is a misrepresentation of this reference to suggest that Slonim suggests that methods of classification

of individuals can and should be practiced without knowledge of the nature of the expression of a target gene. While Slonim does state that the most basic question is which genes expression levels changes, she also discusses at length that this itself is a complicated question. Here, the instant claims are drawn to making a classification of an individual based on the expression of a single gene. All of the methods for classification discussed by Slonim rely on inputted data regarding the exact nature of the change in expression. Slonim teaches that often classification of the a training set may be perfect, but subsequent attempts to classify new test data fail dismally, pointing out that sample prediction from array data is particularly challenging (p. 506).

The instant specification fails to provide a critical piece of information with regard to understanding the relationship between CDCA1 expression and RA. The specification invites one of skill in the art to undertake experimentation to (a) determine the relationship between RA and CDCA1 expression and then to validate that relationship. There is a fundamental absence of information given in the specification. The claims all set forth comparing the test level to "a quantified level of RNA encoded by said gene in blood samples from control subjects..." but the specification does not provide this quantified level, or any quantified level. So, it is left to one of skill in the art to establish what is critical for the practice of the invention. While the specification may rely on the state of the prior art to help enable the invention, the specification may not rely on the state of prior art to supplement what is critical to the practice of the invention- in this case the quantified levels of control RNA encoded by the gene in the control subjects, no matter which type of control subjects.

Applicant points out that the specification teaches the use of classification methods on page 13 of the remarks. The method cited by applicant, as stated in the specification generally

requires a training phase and a testing phase before the classification tool is even developed. Here, the training phase has occurred, but the disclosure of the results is incomplete. Thus, in order to begin to reasonably use such a classification method, one or skill in the art would have to repeat (and validate) the training phase and then complete the testing phase. The outcomes of these phases are not predictable, and there is no guidance in the specification as to what the outcomes will be.

Applicant points out that claims 70 includes comparisons of the test subject to both healthy and RA controls, and not other diseases. Applicant further points out that claims 70 is not disclosed as an unequivocal diagnosis. However, the claims does include step which "classifying" expression and in order for this to have any meaning, the underlying relationship must be predictable. In order for one of skill in the art to determine if this is the case, an inventive amount of experimentation must take place, as discussed in the rejection. Even if the claimed invention is being used as a preliminary tool in a diagnostic process, practicing the invention in realistic setting would require one to know what outcome to expect in order to have some idea if the obtained result is reliable.

Applicant points out that in the Metabolite patent the assay for elevated homocystein levels could signal a risk of heart disease, while the claims of the Metabolite patent set forth that the elevated homocysteine in the body fluid is correlated with a deficiency of cobalamin or folate. Applicant points out that this issue was never raised in litigation regarding the validity of this patent. This is not a persuasive argument. The absence of the argument does not mean that it could not have been a valid point. Further, in this case, the issue of ambiguity of classification is one of many different factors considered to arrive at the conclusion of lack of enablement.

The issue is present and remains present in the context of many other complicated and unpredictable issues, as discussed in the rejection.

The remarks point out that the claims neither claim, seek or require a method for absolute diagnosis or classification of RA, and that an indication is not equated with diagnosis. However, some of the claims do in fact recite "detecting" RA, which suggests that following the method will result in detecting RA, if it is present. Some of the instant claims do not recite or require methods for positively detecting RA, but it is noted that the claims are sufficiently broad so as to encompass methods wherein the practiced method is a method of detecting RA. For example, a method of detecting RA which practiced the steps of claim 66 would certainly be within a broadly interpreted method of identifying an individual as being a candidate for having RA or simply a method for detecting and classifying expression of RA. It is noted, however, that every possible embodiment of a claim does not have to be enabled for the claim to be enabled. Here other issues under 112 first paragraph for lack of enablement persist, as discussed in the rejection and in the response to remarks that follow.

Applicant states that the differential expression of CDCA1 as between subjects having RA and not having RA is predictable (page 16), pointing to the validation experiments carried out by Osman et al. Here no validation has occurred. Further, here there is not complete disclosure of the relationship between the gene expression and RA, so even if one were to attempt to validate the result one would not know if the obtained result were a validation or a contradiction of the findings of applicant.

Applicant disagrees with the contention based on Wu et al. that expression data needs to be interpreted in view of other biological knowledge (page 17). Wu was relied upon for much

more than this simple statement. Wu discusses at length many of the factors that make gene expression analysis unpredictable. Applicant's statement that "differential gene expression which is reproducible, and is correlated with the state of health or disease of the individual does not necessarily result directly in the state of the disease of the individual" is attorney argument which is not supported by evidence on the record. Even if the changes are a result of downstream effects of the pathogenic process, they are related to the state of disease in the individual. Applicant points out that certain prostate markers were used as biomarkers without an understanding of their function. The examiner is not trying to require an understanding of CDCA1 in RA or any other disease, nor does Wu suggest that such is necessary. The examiner is looking to the specification for adequate guidance for making and using an invention in a highly unpredictable field of endeavor.

Applicant states that the unpredictable nature of the technology area as discussed by Wu and Newton are well understood by a person skilled in the art. While it is true that it is well understood by a person of skill in the art that factors such as variability and normalization are important, it is also understood that these add to the unpredictability of the technology. To this end, Newton specifically teaches that replication is essential for providing reliable results. In the instant application a single analysis of two groups was carried out, and the results were not validated in an independent experiment.

Applicant states that the results of Cheung et al. cannot be reliably extrapolated to primary blood samples since Cheung et al. are using cultured cell lines. However, this is irrelevant to the point of Cheung et al. which is that among individuals (in this case cell lines) there is natural variability in gene expression for any particular gene. Attorney arguments are not

sufficient to establish that this biological fact is not the case. Applicant requests support for the examiner's position, that the demonstrating the variability among cell lines is analogous to the variability of blood samples from individuals in general and in particular for the gene CDCA1. The point is that gene expression naturally can vary among individuals, as taught by Cheung et al. This can be a complicating factor contributing to the unpredictability of this technology area. In this case, a single observation has been provided of variability of gene expression among two groups of individuals, without validation. It is agreed that Cheung et al. do not speak to CDCA1 in particular, but the point remains relevant for establishing the unpredictable nature of the technology area. This is but one piece in an analysis that includes many different aspects.

For all of these reasons, the rejection is maintained.

Regarding the 102 rejection over Chittenden, applicant traverses, beginning on page 18 of the response. Applicant states that the office action provides no evidence that CDCA1 was actually detected by Chittenden. The rejection is based on inherency. The reference appears to meet the limitations of the claims- the prior art method has presumptively carried out the same method steps, or very similar method steps as those used in the instant application. The assumption that there were no technical difficulties is based on the fact that none were reported. It is reasonable to assume that the gene was inherently expressed in the blood samples of healthy humans based on applicant's disclosure that this is so. There is a presumption that the routinely practiced prior art process worked as would normally be expected. Thus, the burden has been shifted to applicant to demonstrate that the apparent inherent practice of the claimed invention did not occur. This burden can only be met by providing proper evidence on the record to

overcome the case of inherency. *See In re Best*, 562 F.2d 1252, 1255 (CCPA 1977)("Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, on 'prima facie obviousness under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and is fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products"). On this record, applicants have proffered no such proof. The rejection is maintained.

Applicant traverses the 103 rejection beginning on page 19 of the response.

Applicant states that since neither Maas et al. nor the Affymetrix data sheet teach any relationship between CDCA1 and RA the cited references would only be combined by one having the benefit of Applicant's specification using impermissible hindsight. However, this is not persuasive. Here, one would have been motivated to use the Affymetrix chip to achieve the benefit of screening more gene simultaneously. The knowledge of the relationship between CDCA1 and RA is not required to arrive at the claimed invention since all of the active process steps of the invention are met without this knowledge by the combination of the references. The instant claims are drawn using "comprising" language, and so, while the combined teachings of the references would result in the measuring of expression of many tens of thousands of different genes, CDCA1 is included in these, and so the claim limitations are met. The rejection is maintained. Applicant repeats this argument regarding the rejection under Heller, Affymetrix and Sharma. It is not persuasive in this instance for the same reasons.

Applicant argues that the generic teaching by Sharma is not sufficient motivation to apply the teaching of Heller et al. to detect expression of a CDCA1 gene in blood of a human test subject having RA because Sharma et al. provides no substantive scientific basis to predictably

arrive at the claimed invention of identifying CDCA1 as a candidate marker for RA. Regarding independent claim 58, this claim is not drawn to identifying CDCA1 as a candidate marker for RA, and does not require testing in patients who have RA. So for this claim, and most of the claims that depend from it, this argument is moot because the limitations are not claimed. Further, applicant's argument that there is not sufficient motivation to combine the references is moot in view of KSR which forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. Here, Sharma provides a general motivation to screen the blood for disease markers for any disease as a means for searching for diagnostic tools.

Applicant argues that Sharma's teachings do not necessarily apply to every disease but only to those that lead to alterations in the activity of genes in a pattern which is specific to any particular condition of the organism under observation. Sharma clearly believes that this applies to a diverse set of genes and conditions, in fact virtually all diseases and conditions. Sharma et al. does not provide a single piece of preliminary data, but they do clearly provide from their teaching that markers can be found in the blood.

Applicant argues that in this case the simple substitution of one element for another would not produce a predictable result. However, this is not persuasive. It is entirely predictable that one could have made the suggested tissue substitution and carried out the methods of gene comparison as suggested by the references. All of the techniques are routine. The data collected would have been unpredictable, but the method, which here is the result, could have been predictably practiced. The practice of the predictable method would have inherently resulted in the measuring of CDCA1 expression, and thus, the structural process steps of the claimed

methods are met by the prior art. The instant claims are drawn using "comprising" language, and so, while the combined teachings of the references would result in the measuring of expression of many tens of thousands of different genes, CDCA1 is included in these, and so the claim limitations are met. The rejection is maintained.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Tuesday, or Wednesday, from 9:00 AM until 4:30 PM, and Thursday from 12:15 PM until 5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is

(866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

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